feature

# Extension of quality-by-design concept to the early development phase of pharmaceutical R&D processes

**Ildikó Csóka**, csoka@pharm.u-szeged.hu, **Edina Pallagi and Tamás L. Paál**

**Here, we propose the extension of the quality-by-design (QbD) concept to also fit the early development phases of pharmaceuticals by adding elements that are currently widely applied, but not yet included in the QbD model in a structured way. These are the introduction of a 'zero' preformulation phase (i.e., selection of drug substance, possible dosage forms and administration routes based on the evaluated therapeutic need); building in stakeholders' (industry, patient, and regulatory) requirements into the quality target product profile (QTTP); and the use of modern quality management tools during the composition and process design phase [collecting critical quality attributes (CQAs) and selection of CPPs) for (still laboratory-scale) design space (DS) development. Moreover, during industrial scale-up, CQAs (as well as critical process parameters; CPPs) can be changed; however, we recommend that the existing QbD elements are reconsidered and updated after this phase.**



## Introduction

QbD, as a quality management concept emphasizing the design of quality into products and services, was introduced originally by Juran [1]. After several years of use in different fields, this concept reached the pharmaceutical sector, concurrently with the improvement of quality assurance methods used in pharmaceutical manufacturing. It became clear that prior knowledge of the stakeholders and their expectations of quality, together with the evaluation of risks arising on the way to achieving the targeted product, form a scientific knowledge-based holistic and systematic way of pharmaceutical development [2]. The elements of the QbD methodology are described in the ICH Q8 (R2) international guideline [3].

The 'minimum QbD approach' presented in the guideline comprises the definition of the QTPP and the summary of the main product characteristics, based on the stakeholders' expectations. Moreover, it deals with the identification and determination of the CQAs, followed by the selection of the manufacturing process and the definition of the in-process control strategy. The definition of the CQAs is essential, because they have the most influence on the final product quality and performance characteristics (affecting also safety and efficacy), and need to be controlled.

By contrast, the enhanced QbD approach shows more proactive step-by-step development. It also comprises a risk assessment (RA) and a DS development phase before the definition of the control strategy. The philosophy of continuous quality improvement manifests in the presence of the lifecycle management and continual improvement aspects involved in drug discovery. Quality risk management and pharmaceutical quality system approaches are published in the relevant ICH guidelines (Q9 and Q10) [4,5]. Application of the QbD approach in marketing authorization procedures is both preferred and highly recommended [6–8].

This QbD methodology, with the advantage of promoting a better understanding of the material characteristics and process parameters affecting the final quality of the targeted product, also brings a holistic and risk-based structured way of thinking into industrial manufacturing procedures.




https://doi.org/10.1016/j.drudis.2018.03.012

Here, we emphasize that, with further enlargement with other, already existing tools for a risk-based approach, the above QbD approach could also be used to cover the early phases of pharmaceutical research activities, resulting in the time- and cost-effective transfer from the research phase to market approval and industrial-scale manufacturing. We summarize our experiences of implementing the QbD approach into different dosage form design processes (e.g., [9–12]). In short, with only a partial extension of the enhanced QbD approach described above, an R&D QbD can be created.

## Discussion

Figure 1 shows the enhanced QbD approach, outlined above, complemented by us with the new elements shown in red. These comprise a preformulation ('zero phase') DS phase and the 'a–d boxes'. The first two of these boxes are detailed in Fig. 2.

The preformulation DS means the careful assessment of the available biopharmaceutical knowledge on the multidimensional elements of 'unmet therapeutic needs' (in their broadest meaning) as well as all the possibilities concerning the administration route–dosage form–drug substance triangle (the latter could be synthetic, natural, or biological, inherently different e.g. in terms of their standardization and variability). These initial steps can be labelled as the 'Zero design phase' within the R&D process. As a result of this phase, one can have a 'space' as a basis for the further points to be taken into consideration to achieve the targeted quality product. These interrelations and decisions in this '0 phase' are shown in Box (a) in Fig. 2.

This approach, complemented with a possible benefit and risk assessment, has been successfully used previously. For example, Pallagi *et al*. used this approach during the early development phase of the formulation of nanosized meloxicam powder gel for intranasal administration [9]. The approach also appeared to be used successfully in the development of meloxicam-containing dry powder for inhalation comprising also a process map on the production of a co-micronized (microcomposite) system and the creation of an Ishikawa diagram collecting all the relevant influencing factors. It helped also the authors in the selection of CQAs and the CPP [10]. The Ishikawa diagram and Pareto charts also helped in CQA and CPP selection during the early development of a microparticle-based dry powder inhalation formulation of ciprofloxacin hydrochloride [11]. Furthermore, Kovács *et al*. used this early QbD approach successfully in the formulation development of multiple emulsions for topical use [12].

Box (b) in Figs. 1 and 2 illustrate the basic stakeholders who define the acceptance criteria or share their expectations concerning their

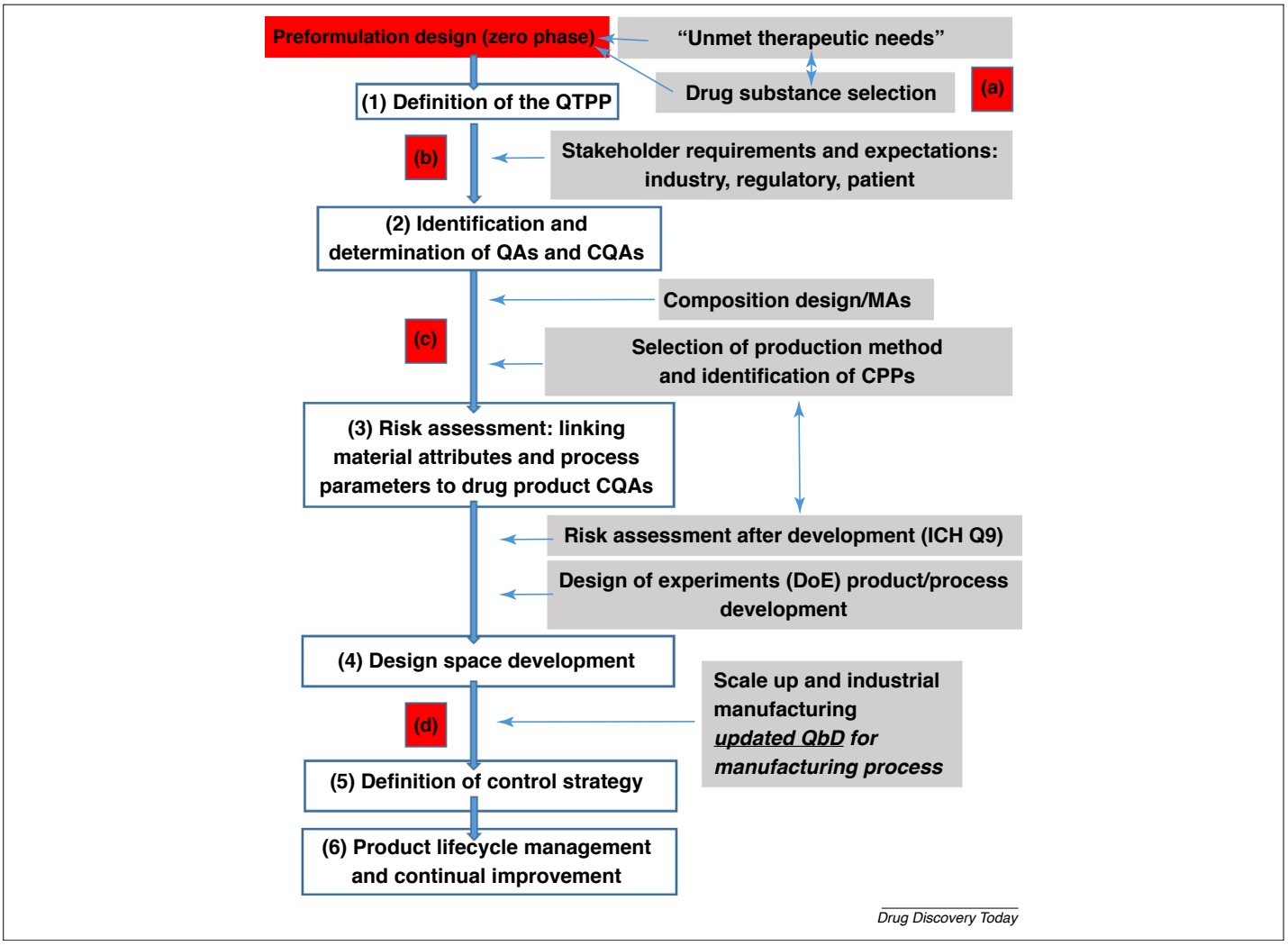


**FIGURE 1**

Proposal for a quality-by-design (QbD) flow chart adopted for the research and development (R&D) stage. Abbreviations: CPPs, critical process parameters; CQAs, critical quality attributes; DoE, design of experiments; MAs, (critical) material attributes; QAs, quality attributes; QTPP, quality target product profile.

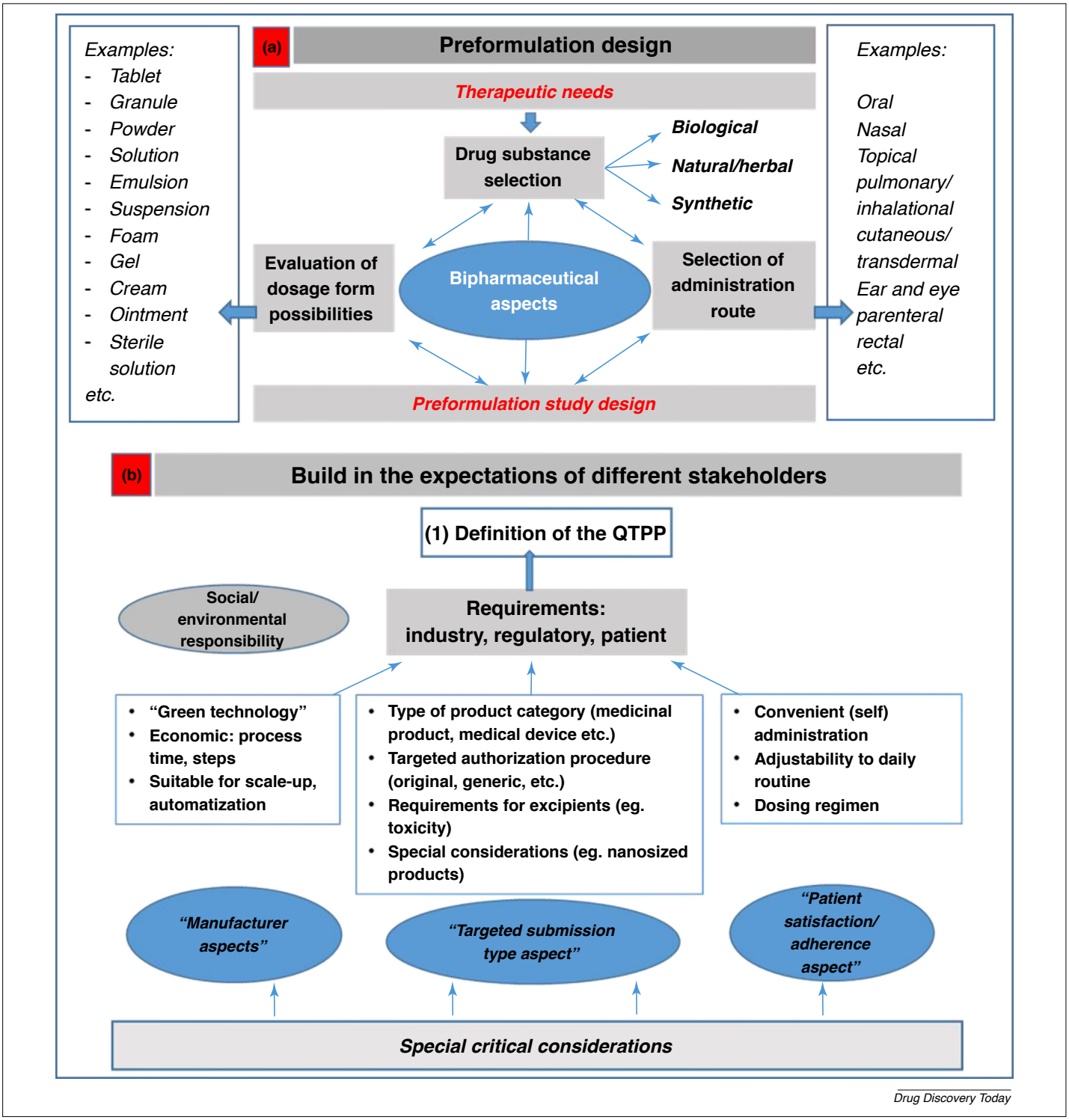


**FIGURE 2**

Interrelations, decisions in the zero phase (a) and the implementation of stakeholders' expectations (b). Abbreviation: QTPP, Quality Target Product Profile.

contribution to the therapy achieved with the given product, depending on their field of interest. Evaluation of these inputs forms the second important part of this new R&D QbD approach. The expanded way of defining the target product profile comprises four aspects. Based on prior knowledge, patient expectations, satisfaction, and adherence are interrelated factors; therefore, all available patient aspects experienced concerning a given therapy, administration route, or dosage form should be fed back into the development process. For instance, combination products, as a rule, improve patient adherence.

Regulatory requirements and their implementation should be also taken into consideration during the early phase of development; in particular, the consequences of the type of the submission are often neglected in the QbD literature. Based on our experience, one should evaluate the already marketed products in the

given therapeutic indication, drug substance type and concentration, dosage form, and so on, to position the product in question properly and choose among the submission types available (e.g., new stand-alone submission); one should also be aware of the limitations of the invention. For a generic submission, the: CQAs of the reference product should be strictly reproduced. However, a well-positioned generic product may also answer unmet therapeutic needs if placed on a market where the originator does not exist. (This explains why the introduction of certain generics can result in a sudden increase in the treated population and, consequently, the environmental exposure [13].)

In terms of the bibliographic or well-established use submission, the relevance of the cited bibliography to the CQAs of one's product should be verified, which is not always easy. For example, in case of Biopharmaceutics Classification System (BCS) II and IV drug substances, it is difficult to prove that the product will be similar to the marketed ones without performing comparative pharmacokinetic studies; however, this is not needed if the drug substance belongs to BCS I or III class (i.e., dissolving within the physiological pH range well).

Stakeholders from the manufacturing industry focus on other aspects of quality and should communicate their expectations, such as costs of manufacturing, scale-up difficulties, and so on. The fourth, relatively new aspect of developing new medicinal products is social responsibility; namely, favoring the different 'green technologies and avoiding toxic and hazardous materials during processing.

After this enlarged decoding of the QTPP, determination of the quality attributes (QAs) and the CQAs forms the next step, followed by the selection of the (critical) material attributes (MAs). These form an integral part of the composition and process design phase together with the determination of the CPPs. The final theoretical composition with a defined preparation methodology includes all the characteristics defined by the above-mentioned four aspects. To collect these influencing and relating factors, several modern quality management tools can be used, including Ishikawa diagrams for evaluating cause–effect relations or the setting up of a decision tree that helps the route selection during the development process, as well as Pareto analysis, which helps identify causes of more frequent problems [10,11]. This is the third 'expansion' of the classical QbD method, and it is indicated by Box (c) in Fig. 1.

Last but not least, the following modification of the classical QbD flow chart is recommended to be performed after the DS development phase. Generally, the DS is determined by applying different factorial design possibilities and the factors identified as being critical are then used in the given formulation development. It is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide an assurance of quality [3,14–17] (i.e., the 'space' where CQAs are met given variations in CPPs within a well-defined domain). This is determined both on a laboratory scale and in the manufacturing environment. However, CPPs (and sometimes MAs) often, and almost inevitably, change during scale-up and/or during the real manufacturing environment. Thus, we recommended reconsidering and updating the existing QbD plan after this phase. This is the fourth expansion and indicated by Box (d) in Fig. 2. (Naturally, reconsideration of CQAs and CPPs form part of the product lifecycle management and continuous improvement stages, which are integral to the QbD approach. However, our experience suggests that the biggest changes in these parameters are expected during scale-up from laboratory to pilot manufacturing scale. This is emphasized in our proposed extension.)

The additional steps provided in Fig. 1 (5 and 6) remain unchanged.

## Concluding remarks

The early (laboratory-scale) development phase of pharmaceuticals, where the QbD approach should be followed, comprises elements that are currently missing from the existing QbD model [6–8]. Introduction of necessary (probably already widely used) elements into the enhanced QbD model could create an R&D QbD that is more suitable for the early development phase of pharmaceutical formulations. Such elements comprise the assessment of unmet therapeutic needs, the choice of drug substance type in correlation with the administration route and dosage form (preformulation study design), building in stakeholder expectations, use of modern risk assessment tools during the experimental (composition) design, then reconsidering and updating as required the resulting (laboratory) DS after manufacturing scale-up.

## References


1 Juran, J.M. (1992) *Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services.* The Free Press

2 Yu, L.X. *et al.* (2014) Understanding pharmaceutical quality by design. *AAPS J.* 16, 771–783

3 ICH (2009) *ICH Harmonised Tripartite Guideline: Pharmaceutical Development Q8 (R2).* ICH

4 ICH (2005) *ICH Harmonised Tripartite Guideline: Quality Risk Management Q9.* ICH

5 ICH (2008) *ICH Harmonised Tripartite Guideline: Pharmaceutical Quality Systems Q10.* ICH

6 Nguyen, M.A. *et al.* (2017) A survey on IVIVC/IVIVR development in the pharmaceutical industry — past experience and current perspectives. *Eur. J. Pharm. Sci.* 102, 1–13

7 Royle, K.E. *et al.* (2013) Integration of models and experimentation to optimise the production of potential biotherapeutics. *Drug Discov. Today* 18, 1250–1255

8 Maniruzzaman, M. and Nokhodchi, A. (2017) Continuous manufacturing via hot-melt extrusion and scale up: regulatory matters. *Drug Discov. Today* 22, 340–351

9 Pallagi, E. *et al.* (2015) Adaptation of the quality by design concept in early pharmaceutical development of an intranasal nanosized formulation. *Int. J. Pharm.* 491, 384–392

10 Pallagi, E. *et al.* (2016) New aspects of developing a dry powder inhalation formulation applying the quality-by-design approach. *Int. J. Pharm.* 511, 151–160

11 Karimi, K. *et al.* (2016) Development of a microparticle-based dry powder inhalation formulation of ciprofloxacin hydrochloride applying the quality by design approach. *Drug Des. Dev. Ther.* 10, 3331–3343

12 Kovacs, A. *et al.* (2016) Optimization and development of stable w/o/w cosmetic multiple emulsions by means of the Quality by Design approach. *Int. J. Cosmet. Sci.* 38, 128–138

13 EMA (2010) *Questions and Answers on 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, EMA/CHMP/SWP/44609/2010 Rev. 1.* EMA

14 Zidan, A.S. *et al.* (2007) Quality by design: understanding the formulation variables of a cyclosporine, a self-nanoemulsified drug delivery systems by Box-Behnken design and desirability function. *Int. J. Pharm.* 332, 55–63

15 Xu, X. *et al.* (2012) A Quality by design (QbD) case study on liposomes containing hydrophilic API: II. Screening of critical variables, and establishment of design space at laboratory scale. *Int. J. Pharm.* 423, 543–553

16 Wu, H. and Khan, M.A. (2009) Quality-by-design (QbD): an integrated multivariate approach for the component quantification in powder blends. *Int. J. Pharm.* 372, 39–48

17 Lendrem, D.W. *et al.* (2015) Lost in space: design of experiments and scientific exploration in a Hogarth Universe. *Drug Discov. Today* 20, 1365–1371



**Ildikó Csóka***
**Edina Pallagi**
**Tamás L. Paál**

*University of Szeged, Faculty of Pharmacy, Institute of Pharmaceutical Technology and Regulatory Affairs, H-6720 Szeged, Eötvös u. 6, Hungary*

**Corresponding author.*